Amendments to the Claims

1. (Withdrawn) A nucleic acid molecule comprising a $P66^{shc}$ coding sequence incorporating at least one mutation as compared to the wild type sequence or the sequence as shown in SEQ ID NO: 1 such that the protein encoded by the coding sequence has at least one serine residue absent or replaced by a different amino acid residue.

2. (Withdrawn) A nucleic acid molecule according to claim 1 wherein the serine residue is selected from the group consisting of S17, S19, S20, S26, S28, S36, S38, S40, S41, S54, S60, S66, S80 and S102.

3. (Withdrawn) A nucleic acid molecule according to claim 1 wherein the serine residue is selected from the group consisting of S28, S36 and S54.

4. (Withdrawn) A nucleic acid molecule according to claim 1 wherein the serine residue is S36 and is replaced by alanine ($p66^{shc}$S36A).

5. (Withdrawn) A polypeptide encoded by a nucleic acid molecule according to claim 1.

6. (Withdrawn) A replicable vector comprising nucleic acid according to claim 1 operably linked to control sequences to direct its expression.

7. (Withdrawn) A host cell transformed with a vector according to claim 6.

8. (Withdrawn) A method of producing a modified $p66^{shc}$ polypeptide comprising culturing a host cell according to claim 7 so that the $p66^{shc}$ polypeptide is produced.

9. (Currently Amended) A method of modulating resistance in cells to oxidative stress by affecting the $p66^{shc}$ signal transduction pathway in a cell, said method comprising ~~the step of~~ contacting said cell with an agent capable of modulating $p66^{shc}$ gene expression, wherein said contact modulates resistance in said cells to oxidative stress relative to untreated cells, and wherein said agent is a nucleic acid molecule capable of hybridizing to a nucleic acid encoding SEQ ID NO: 2, thereby modulating resistance in said cells to oxidative stress.

10. (Previously Presented) A method according to claim 9 wherein said agent ~~is a nucleic acid molecule capable of hybridizing to nucleic acid encoding $p66^{shc}$ thereby reducing or preventing said p66shc thereby reducing or preventing~~ reduces or prevents ~~said~~ $p66^{shc}$ expression.

11. (Withdrawn) A method according to claim 9 wherein said agent is a vector comprising nucleic acid encoding $p66^{shc}$, said vector being capable of incorporating said nucleic acid into the genome of the cell so that the nucleic acid encoding p66shc is expressed in the cell.

12. (Currently amended) A method of increasing resistance in cells to oxidative stress comprising the step of disrupting the $p66^{shc}$ signaling pathway via introduction of a nucleic acid molecule which hybridizes to a nucleic acid encoding SEQ ID NO: 2, thereby disrupting the $p66^{shc}$ signaling pathway, said disruption increasing resistance to oxidative stress in said cells.

13. (Withdrawn) A method according to claim 12 wherein said step of disrupting the $p66^{shc}$ affects the susceptibility of $p66^{shc}$ to phosphorylation.

14. (Withdrawn) A method according to claim 12 wherein said step of disrupting the $p66^{shc}$ pathway causes a mutant $p66^{shc}$ polypeptide to be expressed such that at least one serine residue present in the wild type $p66^{shc}$ is absent or replaced by a different amino acid residue.

15. (Withdrawn) A method according to claim 14 wherein said serine residue is S36 and is replaced by alanine.

16. (Withdrawn) A method according to claim 14 wherein said mutant polypeptide cannot be serine phosphorylated.

17. (Withdrawn) A method according to claim 12 wherein said disruption affects the ability of a serine/threonine kinase, p38 or MAPK to phosphorylate $p66^{shc}$.

18. (Withdrawn) A method according to claim 12 wherein the step of disrupting the p66shc signaling pathway includes contacting the cell with an antibody binding domain capable of specifically binding to the $p66^{shc}$ polypeptide such that its function is disrupted or prevented.

19. (Currently amended) A method according to claim 12 wherein said step of disrupting the $p66^{shc}$ signaling pathway includes disrupting the $p66^{shc}$ gene expression.

20. (Cancelled)

21. (Currently amended) A method according to claim [[20]] 12 wherein the ~~substance~~ nucleic acid is an antisense oligonucleotide capable of hybridizing to the nucleic acid encoding the p66shc polypeptide.

22. (Currently Amended) A method for increasing cellular resistance to oxidative stress comprising ~~administration of~~ administering an effective amount of an agent in a pharmaceutically acceptable carrier, wherein said agent ~~which~~ disrupts $p66^{shc}$ expression or a step in the $p66^{shc}$ signaling pathway ~~in a pharmaceutically acceptable carrier~~ in a cell, wherein said agent is an antisense oligonucleotide capable of hybridizing to a $p66^{shc}$ nucleic acid encoding SEQ ID NO: 2, thereby increasing cellular resistance to oxidative stress.

23. (Cancelled)

24. (Currently Amended) A method according to claim ~~23~~ 22 wherein said antisense oligonucleotide is RNA.

25. (Cancelled)

26. (Withdrawn) A method according to claim 22, wherein said agent is an antibody binding domain capable of specifically binding to a $p66^{shc}$ polypeptide or fragment thereof.

27. (Currently Amended) A method ~~as claimed in~~ according to claim 22 wherein said agent is administered for the treatment of a ~~diseases~~ disease selected from the group consisting of arteriosclerosis, ischemic heart disease, lung emphysema, myocardial infarction, stroke, premature aging, cell senescence, Parkinson's, Alzheimer's, cancers, and vascular complications of diabetes.

28. (Withdrawn) A method of increasing resistance to tumor formation in a tissue comprising the step of increasing the expression of $p66^{shc}$ in said tissue.

29. (Withdrawn) A method according to claim 28 wherein the step of increasing the expression of $p66^{shc}$ includes contacting the tissue with an agent capable of increasing expression of $p66^{shc}$ gene.

30. (Withdrawn) A method according to claim 29 wherein said agent is a transcription factor.

31. (Withdrawn) A method according to claim 29 wherein said agent is a vector comprising nucleic acid encoding $p66^{shc}$ polypeptide said vector being capable incorporating said nucleic acid into the genome the cells of the tissue.

32. (Withdrawn) A method of screening for compounds capable of modulating resistance in cells to oxidative stress by modulating the $p66^{shc}$ signaling pathway comprising contacting a candidate compound with a $p66^{shc}$ expression system; determining the amount of a compound of the signaling pathway; and comparing said amount of the component with the amount of the component in the absence of said candidate compound.

33. (Withdrawn) A method according to claim 32 further comprising the step of preparing a pharmaceutical composition comprising the candidate compound capable of modulating a $p66^{shc}$ pathway and a pharmaceutical acceptable carrier.

34. (Withdrawn) A method according to claim 32 wherein said step of determining the amount of a compound of the signaling pathway is an enzyme activity assay.

35. (Withdrawn) A method according claim 32 wherein said candidate compounds include nucleic acid sequences, antibody binding domains, and protein nucleic acids.

36. (Currently Amended) A method of reducing intracellular levels of reactive oxygen species (ROS) in a cell, said method comprising the step of contacting said cell with an agent capable of inhibiting the expression ~~or activity~~ of a $p66^{shc}$ polypeptide in said cell, wherein said agent is a nucleic acid molecule capable of hybridizing to nucleic acid encoding SEQ ID NO: 2, thereby reducing intracellular levels of ROS.

37. (Previously presented) A method according to claim 36 wherein said ~~agent is a~~ contact with said nucleic acid ~~molecule capable of specifically hybridizing with nucleic acid with the cell which codes for the p665hC polypeptide such that~~ reduces or prevents expression the $p66^{shc}$ polypeptide ~~is reduced or prevented~~.

38. (Withdrawn) A method according to claim 36 wherein the agent is an antibody binding domain capable of specifically binding to the $p66^{shc}$ polypeptide such that its functions are inhibited or prevented.

Claims 39-41 (Canceled)

42. (Withdrawn) A method of determining the presence or absence of a $p66^{shc}$ nucleic acid or a mutant, variant derivative or allele thereof in a biological sample, comprising the step of contacting said sample with a nucleic acid molecule capable of hybridizing specifically with said $p66^{shc}$ nucleic acid or a mutant, variant derivative or allele thereof and determining whether or not hybridization has taken place.

43. (Withdrawn) A method of determining the presence or absence of a $p66^{shc}$ polypeptide or a mutant, variant derivative or allele thereof in a biological sample, comprising the step of contacting said sample with an antibody binding domain capable of binding $p66^{shc}$ or a mutant, variant derivative thereof and determining whether or not binding has taken place.

44. (Withdrawn) An expression system comprising a nucleic acid vector having a $p66^{shc}$ coding sequence or fragment thereof inserted therein.

45. (Withdrawn) A method according to claim 10 wherein said agent is a vector comprising nucleic acid encoding $p66^{shc}$, which when expressed in a cell results in production of $p66^{shc}$.

46. (Currently Amended) [[A]] The method according to claim ~~10~~ 9, wherein the nucleic acid molecule is an antisense oligonucleotide capable of hybridizing to the nucleic acid encoding the $p66^{shc}$ polypeptide.

47. (Currently Amended) The method ~~of~~ according to claim 46, wherein said antisense oligonucleotide is RNA.

Claims 48-51 (Cancelled)

52. (Currently amended) A method according to claim ~~48~~ 9, wherein said agent is administered for the treatment of a disease selected from the group consisting of arteriosclerosis, ischemic heart disease, lung emphysema, myocardial infraction, stroke, premature aging, cell

senescence, Parkinson's, Alzheimer's, cancer, and vascular complications of diabetes.